

Comment on "Statistical Mechanics of Membrane-Protein Conformation: A Homopolymer Model"

In a recent Letter Park and Sung¹ modeled a membrane-protein conformation by grand canonical ensemble approach using a homopolymer model. In this comment I would like to point out that although their model has no serious physical mistake, it is far from biological reality.

The basic scenario of their model is depicted in Fig.1(a). Therefore, they expand the interaction into loops, inclusions and adsorptions. It is unrealistic in four aspects: Firstly, for a real membrane the chemical potential inside and outside the cell should be different. However, this point is not included in their fugacities. Secondly, although real protein sequence is head-tail distinguishable and the authors tried to distinguish it in their calculation (Eq. (6)), however, their mathematical model does not include this effect because Q_S , Q_L and Q_H are only classical numbers which are commutable. Thirdly, They consider adsorptions and inclusions to be of the same order processes. However, it is questionable because the number of hydrogen bonds involved in an inclusion can vary. Furthermore, the last diagram in their Fig.2 is unlikely to happen because it requires much too high total free energy, i.e. include entropy effects, to activate. Fourthly, and most importantly, their model is inconsistent with a three-dimensional structural finding, to a resolution of 1.9\AA , of the α -hemolysin pore almost two years ago².

The first point is alright as a first order approximation of the cellular environment. However, the second point is mathematically wrong. On the other hand, the structural finding told us that protein should look like sperms with a big 'head' which consists of about 80% of the total amino acids. Therefore, the head-tail distinguishability is important. It can be considered as a collective partition function different from the partition function of the other part of the protein chain. Furthermore, the 'tail' (in the authors' terminology) is unlikely to form a second adsorption on the membrane surface. It should be folded back to itself to form a 'head' instead, if one thinks in terms of linear polymers.

The structural finding told us that protein aggregates to form a pore due to several protein's tail penetrating the membrane (Fig.1b) instead of one protein chain winding back and forth on the membrane (Fig.1a). These protein units are bound together because of extensive hydrophobic and hydrophilic contacts of their heads. Specifically, for the sample studied in Ref.2, it is seven pieces gathered together to form a mushroom-like pore. The reader should consult Ref.2 for better illustrations and thorough explanation.

In conclusion it turns out nature operates much more efficiently than the authors expected. The structural finding told us that protein penetrating the membrane

only as a 'zeroth order' process in the authors' formulation, i.e., only single inclusion and single adsorptions are possible. Furthermore, these two processes actually happen in sequence. They are not separate processes. Therefore there will not have the problem about which one have higher energy.

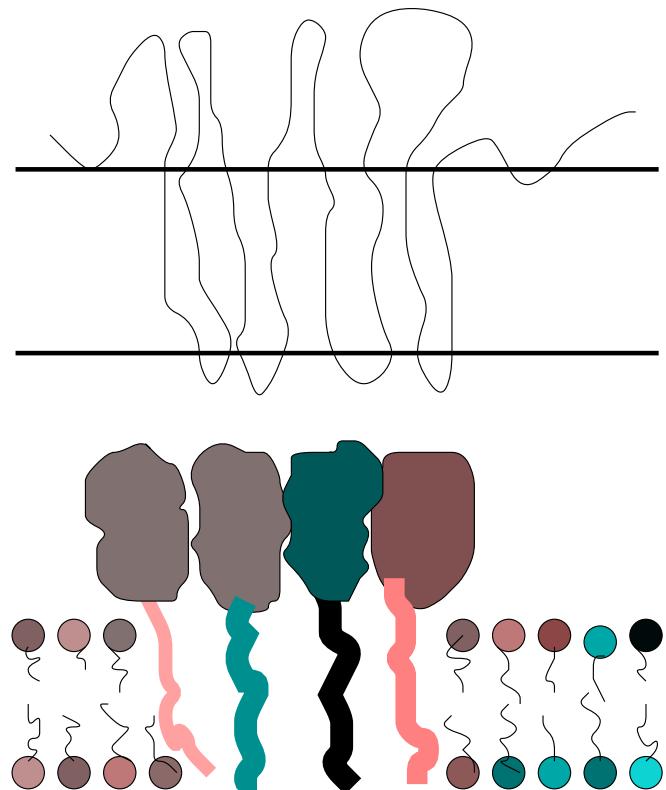


FIG. 1. (a) People thought membrane-protein interacts like chop-sticks and spaghetti. But how could such high order interactions happen in nature? (b) With better resolution, structural finding has resolved definitely that the interaction is only 'zeroth order', but with many protein units.

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